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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,440	FRADET ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-69* is/are rejected.

7)☒ Claim(s) *56* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 12/22/06 in response to the Office Action of 6/23/06 are acknowledged and have been entered.

Claims 1-40 were cancelled by Applicant.

Claims 41-69 have been added by Applicant and are currently under examination.

The following Office Action contains NEW GROUNDS of rejections.

NEW OBJECTIONS

Claim 56 is objected to for an apparent typographical error. Claim 56 recites: "...wherein said PSAmolecular beacon...". It is suspected applicant intended claim 56 to recite: "...wherein said PSA_molecular beacon...". Proper correction is required.

NEW REJECTIONS

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 and dependent claims 42-66 are rejected because claim 41 recites a method for determining a predisposition for or the presence of prostate cancer comprising detecting PCA3 mRNA sequences and "...(d) correlating a detection of said PCA3 mRNA sequence or a level thereof, as compared to a PCA3 mRNA or level thereof associated with normal or non-malignant prostate state, with a risk of developing prostate cancer or a presence of prostate cancer in said patient...". The conclusionary statements of claim 41 do not fully relate back to the preamble of the claim. It is unclear how a measured level is going to be compared to "a PCA3 mRNA sequence". One of skill in the art would not know how to compare a detected mRNA sequence or a level thereof, to "a PCA3 mRNA". Further, it is unclear what kind of level is indicative of what *kind of risk* of developing prostate cancer or with *what kind* of presence of prostate cancer. The claimed method involves the active step of "correlating"; however, it does not recite of what a specific correlation or comparison is *indicative*. It is unclear what kind of detection level, as compared to a PCA3 mRNA or level thereof associated with normal or non-malignant prostate state, would be *indicative* of a particular risk of developing prostate cancer or a presence of prostate cancer in a patient. This renders the claims indefinite. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 41 and dependent claims 42-66 are rejected because claim 41 recites a method for determining a predisposition for or the presence of prostate cancer comprising detecting mRNA sequences and "...(e) correlating an absence of detection

of said PCA3 mRNA sequence or lower level thereof, as compared to a PCA3 mRNA sequence or a level thereof associated with a normal or non-malignant prostate state, with an absence of prostate cancer or a lower risk of developing same, when said second prostate-specific mRNA is detected". The conclusionary statements of claim 41 do not fully relate back to the preamble of the claim. It is unclear how a measured level is going to be compared to "a PCA3 mRNA sequence". One of skill in the art would not know how to compare a detected mRNA sequence or a level thereof, to "a PCA3 mRNA". Further, it is unclear what kind of detection level, as compared to a level thereof associated with a normal or non-malignant prostate state, would be *indicative* of a normal or non-malignant prostate state of a patient when said second prostate-specific mRNA is detected. The claimed method involves the active step of "correlating"; however, it does not recite of what a specific correlation or comparison is *indicative*. It is unclear what kind of detection level, as compared to what, would be *indicative* of an absence of prostate cancer or a lower risk of developing same, when said second prostate-specific mRNA is detected. This renders the claims indefinite. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 63 is rejected for reciting "...a voided urine sample from a patient having an increased number of prostate cells therein". However, the claim does not recite as compared to what said number is increased. This renders the claims indefinite. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 67 and dependent claims 68-69 are rejected because claim 67 recites a method for determining a predisposition for or the presence of prostate cancer comprising detecting mRNA sequences and "...(d) correlating a higher detection of said PCA3 mRNA, as compared to a predetermined cut off value associated with a normal or non-malignant prostate state, with a risk of developing prostate cancer or a presence of prostate cancer in said patient...". The conclusionary statements of claim 67 do not fully relate back to the preamble of the claim. The claimed method involves the active step of "correlating"; however, it does not recite of what a specific correlation or comparison is *indicative*. It is unclear of what kind of risk of developing prostate cancer (higher or lower?) or what kind of presence of prostate cancer in a patient a higher detection of PCA3 mRNA, as compared to a predetermined cut off value associated with a normal or non-malignant prostate state, would be *indicative*. This renders the claims indefinite. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 67 and dependent claims 68-69 are rejected because claim 67 recites a method for determining a predisposition for or the presence of prostate cancer comprising detecting mRNA sequences and "...(e) correlating an absence of detection or lower detection of said PCA3 mRNA, as compared to said predetermined cut off value associated with a normal or non-malignant prostate state, with an absence of prostate cancer or a lower risk of developing same, when said second prostate-specific mRNA is detected". The conclusionary statements of claim 67 do not fully relate back

to the preamble of the claim. The claimed method involves the active step of "correlating"; however, it does not recite of what a specific correlation or comparison is *indicative*. It is unclear of what an absence of detection lower detection of PCA3 mRNA, as compared to a predetermined cut off value associated with a normal or non-malignant prostate state, would be *indicative*. This renders the claims indefinite. Given the above reasons, the metes and bounds of the claims cannot be determined.

35 USC § 112, first paragraph (Written Description Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of "second" prostate-specific mRNA and a genus of molecular beacons (see claim 52). However, the written description in this case sets forth PSA as an example of a "second" prostate-specific mRNA (see claim 45) and a polynucleotide comprising SEQ ID NO:6 and polynucleotides comprising SEQ ID NO:5 as examples of molecular beacons (see claim 53).

The art has identified PSA as a prostate-specific mRNA (see anticipation rejections below). However, based on the structure of an mRNA sequence, the state of the art is such that one of skill would not know whether said mRNA sequence is a prostate-specific mRNA. Further, one of skill in the art would recognize that a "molecular beacon" reads on *any* polynucleotide sequence.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of mRNAs or molecular beacons that encompass the genera nor does it provide a description of structural features that are common to the genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the

genera, and because the genera are highly variant, the disclosure of PSA and SEQ ID NO:6 is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a "second" prostate-specific mRNA wherein said "second" prostate-specific mRNA is PSA, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Further, only a molecular beacon wherein said molecular beacon is a polynucleotide comprising SEQ ID NO:6 or SEQ ID NO:5, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, first paragraph (Enablement Rejection)

Claims 41-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) performing an RNA amplification assay on a urine sample of said patient comprising at least one prostate cell, or nucleic acid extract thereof, using a first primer pair specific to a prostate cancer specific PCA3 mRNA sequence selected from the group consisting of: (i) a polynucleotide comprising SEQ ID NO:9, 10, or 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide fully complementary to (i) or (ii); (b) performing a second RNA amplification assay on said urine sample comprising at least one prostate specific cell, or nucleic extract thereof, using a second primer pair specific to PSA mRNA; (c) detecting said PCA3 mRNA sequence and said PSA mRNA; (d) wherein an increased

level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a normal subject, indicates that said patient will develop prostate cancer or that said patient has prostate cancer; and (e) wherein an absence of PCA3 mRNA or a lower level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a normal subject, indicates that said patient will not develop prostate cancer and that said patient does not prostate cancer, when PSA mRNA is detected, the specification does not reasonably provide enablement for a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) performing an RNA amplification assay on a urine sample of said patient comprising at least one prostate cell, or nucleic acid extract thereof, using a first primer pair specific to a prostate cancer specific PCA3 mRNA sequence selected from the group consisting of: (i) a polynucleotide comprising SEQ ID NO:9, 10, or 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide fully complementary to (i) or (ii); (b) performing a second RNA amplification assay on said urine sample comprising at least one prostate specific cell, or nucleic extract thereof, using a second primer pair specific to "a second prostate-specific mRNA"; (c) detecting said PCA3 mRNA sequence and said second prostate-specific mRNA; (d) correlating, in just any way, a detection of said PCA3 mRNA sequence or any level thereof, as compared to a PCA3 mRNA or a level thereof associated with a normal or non-malignant prostate state with any type of risk of developing prostate cancer or any type of presence of prostate cancer in said patient; and (e) correlating, in just any way, an absence of detection of said PCA3 mRNA

sequence or lower level thereof, as compared to a PCA3 mRNA sequence or a level thereof associated with a normal or non-malignant prostate state, with an absence of prostate cancer or a lower risk of developing the same, when said second prostate-specific mRNA is detected. Further, the specification does not reasonably provide enablement for a method of "...(d) correlating, in just any way, a higher detection of said PCA3 mRNA, as compares to a predetermined cut off value associated with a normal or non-malignant prostate state, with just any type of risk of developing prostate cancer or any type of presence of prostate cancer in said patient; and (e) correlating, in just any way, an absence of detection or lower detection of said PCA3 mRNA, as compared to said predetermined cut off value associated with a normal or non-malignant prostate state, with an absence of prostate cancer or a lower risk of developing same, wherein said second prostate-specific mRNA is detected. Further, the specification does not provide enablement for detecting PCA3 with just any molecular beacon (claim 52). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification discloses (pages 34-40, in particular) a method for determining a predisposition for and the presence of prostate cancer in a patient comprising contacting polynucleotides from a patient's *urine, blood, or prostate biopsy* sample and polynucleotides from a corresponding *control urine, blood, or prostate biopsy* sample from a patient that does not have prostate cancer with oligonucleotides that hybridize under *high stringency* to a polynucleotide sequence within SEQ ID NO:9, 10, or 13 and contacting said samples with oligonucleotides that hybridize under *high stringency* to the polynucleotide encoding PSA, detecting the *presence* of a polynucleotide encoding PSA with a molecular beacon the binds *with high stringency* to the polynucleotide encoding PSA and detecting the *amount* of polynucleotides comprising SEQ ID NO:9, 10, or 13 with molecular beacons that hybridize *with high stringency* to amplification products from SEQ ID NO:9, 10, or 13, wherein the detection of polynucleotides encoding PSA and an elevation in levels of polynucleotides comprising SEQ ID NO:9, 10, or 13 in the patient sample, as compared to the control sample, is indicative of a predisposition for and the presence of prostate cancer.

In regards to methods comprising using a second primer pair specific to "a second prostate-specific mRNA" (see Written description rejection), the specification does not provide a written description of "second" prostate specific mRNAs. Therefore, the specification is not enabling for detecting the broad genus of "second" prostate-specific mRNAs.

Further, claims drawn to "correlating" mRNA expression levels to the presence, absence, or predisposition to a diseased state, broadly reads on mRNA expression levels being indicative of either the presence or absence of said diseased state or predisposition thereto.

Further, claims drawn to mRNA expression levels relating to a "risk" of developing prostate cancer broadly read on mRNA expression levels being indicative of either a "high risk" or "low risk".

Further, it is unclear how a measured level is going to be compared to "a PCA3 mRNA sequence". One of skill in the art would not know how to compare a detected mRNA sequence or a level thereof, to "a PCA3 mRNA".

Further, one of skill in the art would understand that not every molecular beacon would recognize PCA3 mRNA, as the term "molecular beacon" broadly reads on any polynucleotide sequence (see Written Description rejection).

Further, the level of unpredictability for the detection of any disease is quite high. The state of the prior art dictates that if a molecule such as a PCA3 polynucleotide is to be used as a surrogate for a diseased state in conjunction with a marker for PSA polynucleotides, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotides to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research

must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Absent evidence of the polynucleotides' expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polynucleotides in any diagnostic setting without undue experimentation. While the instant specification is enabling for a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) performing an RNA amplification assay on a urine sample of said patient comprising at least one prostate cell, or nucleic acid extract thereof, using a first primer pair specific to a prostate cancer specific PCA3 mRNA sequence selected from the group consisting of: (i) a polynucleotide comprising SEQ ID NO:9, 10, or 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide fully complementary to (i) or (ii); (b) performing a second RNA amplification assay on said urine sample comprising at least one prostate specific cell, or nucleic extract thereof, using a second primer pair specific to PSA mRNA; (c) detecting said PCA3 mRNA sequence and said PSA mRNA; (d) wherein an increased level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a normal subject, indicates that said patient will develop prostate cancer or that said patient has prostate cancer; and (e) wherein an absence of PCA3 mRNA or a lower level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a normal subject, indicates that said patient will not develop prostate cancer and that said patient does not prostate cancer, when PSA mRNA is

detected, the specification has not demonstrated that just any prostate-specific mRNA can be used in place of PSA. Further, the specification has not demonstrated that detection of said PCA3 mRNA sequence or any level thereof, as compared to a level associated with a normal or non-malignant prostate state, correlates in every way with every type of risk of developing prostate cancer and every type of presence of prostate cancer in said patient; and an absence of detection of said PCA3 mRNA sequence or lower level thereof, as compared to a PCA3 mRNA sequence or a level thereof associated with a normal or non-malignant prostate state, correlates in every way with an absence of prostate cancer or a lower risk of developing the same, when a prostate-specific mRNA is detected. A practitioner wishing to practice the broadly claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) performing an RNA amplification assay on a urine sample of said patient comprising at least one prostate cell, or nucleic acid extract thereof, using a first primer pair specific to a prostate cancer specific PCA3 mRNA sequence selected from the group consisting of: (i) a polynucleotide comprising SEQ ID NO:9, 10, or 13; (ii) a polynucleotide sequence that hybridizes under high stringency conditions to the polynucleotide sequence in (i); and (iii) a polynucleotide fully complementary to (i) or (ii); (b) performing a second RNA amplification assay on said urine sample comprising at least one prostate specific cell,

or nucleic extract thereof, using a second primer pair specific to "a second prostate-specific mRNA"; (c) detecting said PCA3 mRNA sequence and said second prostate-specific mRNA; (d) correlating, in just any way, a detection of said PCA3 mRNA sequence or any level thereof, as compared to a PCA3 mRNA or a level thereof associated with a normal or non-malignant prostate state with any type of risk of developing prostate cancer or any type of presence of prostate cancer in said patient; and (e) correlating, in just any way, an absence of detection of said PCA3 mRNA sequence or lower level thereof, as compared to a PCA3 mRNA sequence or a level thereof associated with a normal or non-malignant prostate state, with an absence of prostate cancer or a lower risk of developing the same, when said second prostate-specific mRNA is detected, and Applicant has not enabled said method because: (1) Applicant has not provided a written description of the genus of prostate-specific mRNA, (2) it has not been shown that just any prostate-specific mRNA can be used in place of PSA, (3) the specification has not demonstrated that detection of said PCA3 mRNA sequence or any level thereof, as compared to a level associated with a normal or non-malignant prostate state, correlates in every way with every type of risk of developing prostate cancer and every type of presence of prostate cancer in said patient, and (4) it has not been shown that an absence of detection of said PCA3 mRNA sequence or lower level thereof, as compared to a PCA3 mRNA sequence or a level thereof associated with a normal or non-malignant prostate state, correlates in every way with an absence of prostate cancer or a lower risk of developing the same, when a prostate-specific mRNA is detected. Further, (5) the specification does not provide enablement

for detecting PCA3 with just any molecular beacon (claim 52) and it is clear that every molecular beacon would not detect PCA3.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41-50, 57, 58, 61-63, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Clements et al (The Journal of Urology, 4/99, 161: 1337-1343).

Bussemakers et al teaches a sequence corresponding to PCA3, SEQ ID NO:6, that is 99.5% homologous to instant SEQ ID NO:9 and shares 99.6% local similarity to the first 2036 amino acids of instant SEQ ID NO:9 (see sequence comparisons). SEQ ID NO:6 is 100% identical to instant SEQ ID NO:10 (see sequence comparisons). SEQ ID NO:6 is 89.1% homologous to instant SEQ ID NO:13 and shares 99.6% local similarity to the first 3582 polynucleotides of instant SEQ ID NO:13 (see sequence comparisons). Due to the high degree of homology between SEQ ID NO:6 and instant SEQ ID Nod 9, 10, and 13, one of skill in the art would recognize that complements of SEQ ID NO:6 would hybridize to instant SEQ ID NOs 9, 10, and 13. Bussemakers et al further teaches a method for determining a predisposition for or the presence of prostate cancer in a patient comprising (a) performing an RT-PCR RNA amplification assay on a prostate biopsy sample comprising at least one prostate cell of said patient, or nucleic acid thereof, using a first primer pair specific to SEQ ID NO:6, (b) performing a second RT-PCR RNA amplification assay on said sample using a second primer pair specific to PSA, (c) detecting in said sample an amount of PCA3 and PSA mRNA; and (d) wherein an increased level of PCA3 mRNA, as compared to the level of PCA3 mRNA in a urine sample from a normal subject, indicates that said patient will develop prostate cancer or that said patient has prostate cancer; and (e) wherein an absence of PCA3 mRNA or a lower level of PCA3 mRNA, as compared to the level of PCA3 mRNA

in a sample from a normal subject, indicates that said patient will not develop prostate cancer and that said patient does not prostate cancer, when PSA mRNA is detected (Example 2, in particular). Further, without claiming any stringency of hybridization, PSA would hybridize to kallikrein 2. Bussemakers further teaches a method wherein said amplification assay is TMA (column 37, in particular). Bussemakers further teaches a method wherein said amplification of PCA3 and said PSA mRNA is performed simultaneously (column 36, in particular). Bussemakers further teaches a method wherein said detection is performed by chemiluminescence (paragraph bridging columns 15-16, in particular). By teaching PSA mRNA is detected in both benign and malignant prostate samples and that the level of PSA mRNA is not a reliable indicator of prostate cancer disease state, Bussemakers teaches a method wherein detection of PSA would validate a negative result for PCA3 detection in that the detection of PSA mRNA is indicative of the presence of prostate cells in a sample that did not display elevated PCA3 levels (Example 2, in particular). Bussemakers further teaches a method wherein RNA is extracted using a target capture method (Example 2, in particular). Bussemakers further teaches a method wherein said detection of PCA3 is carried out using chemiluminescent labels in a homogenous detection method (see paragraph bridging pages 15-16 and Example 2, in particular). Bussemakers further teaches a method wherein said amplification of PCA3 and said second prostate specific nucleic acid is performed simultaneously in one container (see column 36, in particular).

Bussemakers does not specifically teach methods using a urine sample, a voided urine sample from a patient having an increased number of prostate cells therein, a

urine sample containing semen, or a urine sample collected following a digital rectal exam. However, these deficiencies are made up in the teachings of Clements et al.

Clements et al teaches a method of using RT-PCR to detect PSA mRNA as a selective marker of prostate cells in urine from normal and prostate cancer patients (see abstract, in particular). Clements et al further teaches methods of using RT-PCR to detect prostate cells in urine containing semen, which was collected as the first urinary void immediately after masturbation, from normal and prostate cancer patients (left column of page 1338, in particular). As compared to the female urine samples obtained by Clements et al, male urine samples had an increased number of prostate cells (left column of page 1339, in particular). Clements et al further teaches methods using urine samples from patients that have had digital rectal exams (left column of page 1338, in particular). Clements et al further teaches that PSA mRNA expression is intended to be used as a marker for prostate cells when screening patients for mRNA markers that are upregulated in prostate cancer cells of patients with prostate cancer (see paragraph flanking pages 1340-1341, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use male urine containing semen that was collected following a digital rectal exam, as taught by Clemens et al, as the sample of the method taught by Bussemakers et al because one of skill in the art would recognize that a digital rectal exam would be used as a quick method to screen for prostate cancer and obtaining male urine containing semen that was collected following said digital rectal exam is less unpleasant and invasive than collecting a prostate biopsy (left column of page 1337 of

Clements et al, in particular). In addition to reasons obvious from the teachings of Bussemakers et al, one of skill would have been further motivated to use PSA mRNA as a marker for prostate cells when screening for PCA3 mRNA in urine containing semen that was collected following a digital rectal exam because Clemens et al teaches that PSA mRNA expression is intended to be used as a marker for prostate cells when screening patients for mRNA markers that are upregulated in patients with prostate cancer (see paragraph flanking pages 1340-1341, in particular) and Bussemakers et al teaches PCA3 demonstrates 20-fold overexpression in prostate cancer cells as compared to PCA3 expression levels in prostate cells from patients without prostate cancer (column 37 of Bussemakers et al, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using male urine containing semen that was collected following a digital rectal in detecting PCA3 mRNA and PSA in the method taught by Bussemakers et al because Clements et al teaches a method of detecting mRNA expressed by normal prostate cells and prostate cancer cells in male urine containing semen that was collected following a digital rectal exam (pages 1338-1339, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim Rejections - 35 USC § 103

Claims 41-50, 57, 58, 61-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of

Clements et al (The Journal of Urology, 4/99, 161: 1337-1343), in further view of Cheung et al (Journal of Clinical Microbiology, 10/94, 2593-2597).

The teachings of Bussemakers et al in view of Clements et al are discussed above.

The combined teachings of Bussemakers et al in view of Clements et al do not specifically teach methods of extracting RNA using a silica-based method. However, these deficiencies are made up in the teachings of Cheung et al.

Cheung et al teaches a method of extracting RNA from a sample using a silica-based method (pages 2593-2594, in particular). Cheung et al further teaches that the silica-based method is at least as sensitive and in certain circumstances more sensitive than traditional phenol-chloroform extraction (page 2593, in particular). Cheung et al further teaches that this improved sensitivity may be due to more efficient recovery by silica particles (page 2593, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to extract RNA using a silica based method, as taught by Cheung et al, when obtaining the RNA for the method taught by combined teachings of Bussemakers et al in view of Clements et al because Cheung et al teaches silica-based methods of RNA purification are at least as sensitive and in certain circumstances more sensitive than traditional phenol-chloroform extraction (page 2593, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for extracting RNA using a silica based method when obtaining the RNA in the methods taught by the combined teachings of Bussemakers et al in view

of Clements et al because Cheung et al teaches how to extract RNA using a silica based method (pages 2593-2594, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim Rejections - 35 USC § 103

Claims 41-50, 57, 58, 59-63, and 65-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Clements et al (The Journal of Urology, 4/99, 161: 1337-1343), and in further view of Baret (EP 0 256 932 A2; 2/24/88).

The teachings of Bussemakers et al in view of Clements et al are discussed above.

The combined teachings Bussemakers et al in view of Clements et al does not specifically teach methods of chemiluminescent detection using acridinium ester compounds.

Baret teaches methods of chemiluminescent detection using acridinium ester compounds (page 4, in particular). Further, Baret teaches methods of chemiluminescent detection using acridinium ester compounds are particularly useful for nucleotide probe analysis because they provide very stable signals that are measurable for long periods of time (page 3, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the chemiluminescent detection of PCA3, as taught by the

combined teachings Bussemakers et al in view of Clements et al, using acridinium ester compounds because Baret teaches methods of chemiluminescent detection using acridinium ester compounds are particularly useful for nucleotide probe analysis because they provide very stable signals that are measurable for long periods of time (page 3, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing the chemiluminescent detection of PCA3, as taught by the combined teachings Bussemakers et al in view of Clements et al, using acridinium ester compounds because Baret teaches methods of chemiluminescent detection using acridinium ester compounds (page 4, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim Rejections - 35 USC § 103

Claims 41-51, 54, 57, 58, 61-63, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Clements et al (The Journal of Urology, 4/99, 161: 1337-1343), in further view of Buck et al (1999, Biotechniques, 27(3):528-536).

The teachings of Bussemakers et al in view of Clements et al are discussed above.

The combined teachings Bussemakers et al in view of Clements et al does not specifically teach a method comprising detecting PCA3 using a primer pair comprising

SEQ ID NOs: 3 and 4 or a method comprising detecting PSA using a primer pair comprising SEQ ID NOs: 1 and 2. However, these deficiencies are made up in the teachings of Buck et al.

Buck et al teaches a study wherein 69 different primer sequences were submitted by 39 different laboratories and 95 control primers distributed at 3 base pair intervals across a 300 base pair oligonucleotide test sequence were analyzed (pages 528-529, in particular). It was determined that all the submitted primers functioned very well and almost all the "control" primers functioned very well (page 533). Only one the "control" primers functioned poorly; however, the poorly performing control primer performed adequately under optimized conditions (page 533). Thus, under optimal sequencing conditions with highly pure template and primer, many of the commonly applied primer design parameters are dispensable (see page 528, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method taught by the combined teachings Bussemakers et al in view of Clements et al by using a primer pair comprising SEQ ID NOs: 3 and 4 to detect PCA3 and a primer pair comprising SEQ ID NOs: 1 and 2 to detect PSA because Buck et al teaches that, due to the new generation of sequencing reagents (page 528, in particular), any sequences throughout a known oligonucleotide would be obvious choices to design a primer. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing the method taught by the combined teachings Bussemakers et al in view of Clements et al by using a primer pair comprising SEQ ID NOs: 3 and 4 to detect PCA3 and a primer pair

comprising SEQ ID NOs: 1 and 2 to detect PSA because Bussemakers et al teaches a method of using primers to detect PSA and PCA3 (Example 2, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim Rejections - 35 USC § 103

Claims 41-50, 52, 53, 55, 56, 57, 58, 61-63, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussemakers et al (US 7,008,765 B1; filed 4/9/98) in view of Clements et al (The Journal of Urology, 4/99, 161: 1337-1343), in further view of Schlegel et al (US 2002/0168638 A1; filed 1/24/01).

The teachings of Bussemakers et al in view of Clements et al are discussed above.

The combined teachings Bussemakers et al in view of Clements et al does not specifically teach methods of using a molecular beacon to detect PCA3, using a molecular beacon to detect PSA, using a molecular beacon comprising SEQ ID NO:6 to detect PCA3, or using a molecular beacon comprising SEQ ID NO:5 to detect PSA. However, these deficiencies are made up in the teachings of Schlegel et al (US 2002/0168638 A1; filed 1/24/01).

Schlegel et al teaches methods of detecting prostate cancer comprising detecting PCA3 polynucleotides and PSA (paragraph 161, in particular). Schlegel et al further teaches methods of detecting markers of prostate cancer comprising using molecular beacons (paragraph 216, in particular). Schlegel et al further teaches that molecular

beacons are useful for quantitating the presence of nucleic acids in a sample (paragraph 216, in particular). Schlegel et al further teaches methods wherein the biological sample is urine (paragraph 12 and 150, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method taught by the combined teachings of Bussemakers et al in view of Clements et al using any molecular beacon specific for PCA3 mRNA, including one comprising SEQ ID NO:6, and any molecular beacon to detect PSA mRNA, including one comprising SEQ ID NO:5, because Bussemakers et al teaches the polynucleotide sequences of PCA3 and PSA, rendering any molecular beacon comprising any SEQ ID NO that would detect PCA3 or PSA obvious, and Schlegel et al further teaches that molecular beacons are useful for quantitating the presence of nucleic acids in a sample (paragraph 216, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining using molecular beacons to detect PCA3 and PSA in the method taught by the combined teachings Bussemakers et al in view of Clements, including those comprising SEQ ID NO:5 and those comprising SEQ ID NO:6, because Schlegel et al teaches methods of detecting markers of prostate cancer comprising using molecular beacons (paragraph 216, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

NEW MATTER

Claim 66 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claim 66 recites: "The method of claim 63, wherein said urine sample contains semen". Descriptions of urine samples containing semen are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Claims 41 and dependent claims 42-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claim 41 recites: "...correlating a detection of said PCA3 mRNA sequence or a level thereof, as compared to a PCA3 mRNA... correlating an absence of detection of said PCA3 mRNA sequence or lower level thereof, as compared to a PCA3 mRNA". Descriptions of comparing levels or "detections" of PCA3 mRNA to "a PCA3 mRNA" are

not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600